REMARKS

Reconsideration and withdrawal of the rejections of the June 16, 2005 Office Action is respectfully requested in view of the remarks and amendments herewith.

I. STATUS OF THE CLAIMS AND FORMAL MATTERS

Claims 1, 3-4, 9, 11-48 and 50-75 are now pending. Claims 1, 4, 12, 29, 46, 56 and 75 have been amended, and claims 6-8 and 49 have been cancelled, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

No new matter is added.

It is submitted that these claims are and were in full compliance with the requirements of 35 U.S.C §112. In addition, the amendment and remarks herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§101, 102, 103 or 112; but rather the amendments and remarks herein are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Support for the amended claims is found throughout the specification and the original claims.

II. REINSTATEMENT OF ELECTION OF SPECIES

The Office Action states that the election of species requirement has been reinstated. Applicants respectfully traverse this reinstatement, and request that the original withdrawal of the requirement in the August 27, 2004 Office Action be maintained. To this end, the arguments against the election of species put forth by Applicants in the response filed January 22, 2004 are incorporated herein in their entirety. However, should the election of species requirement not be withdrawn, Applicants reiterate their election, with traverse, of the species comprising tumor cells, malignant cells and leukemia cells.

III. THE OBJECTIONS TO THE CLAIMS ARE OVERCOME

Claims 4 and 49 were objected to under 37 C.F.R. §1.75 because claim 49 is allegedly a substantial duplicate of claim 4. Applicants have cancelled claim 49 herein, such that the objection is now moot. Accordingly, reconsideration and withdrawal of the objections to the claims is respectfully requested.

IV. THE REJECTIONS UNDER 35 U.S.C. §112 ARE OVERCOME

Claims 1, 3, 4, 6, 9, 11-18, 23, 24, 25-39, 46-49, 52-75 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Office Action alleged that a sufficient number of species of "small molecules" were not described in the specification to provide full descriptive support of the genus encompassing all such molecular adjuvants. Applicants maintain their traversal of this rejection, however, in order to advance prosecution, Applicants have amended the claims herein to specify that the "small molecules" are biotin and avidin/streptavidin or calmodulin and calmodulin binding peptides.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 29 and 75 were also rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for lacking antecedent basis for the recitation "one or more" of the "compositions." The rejection is respectfully traversed.

Claims 29 and 75 have been amended herein to correct the antecedent basis of the claims. Accordingly, the rejection is now moot.

Claims 6-8, 12 and 56 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The rejection is respectfully traversed.

Specifically, claims 6-8 each recited "comprises a three-step chain of small molecules," which was considered to lack antecedent basis. Each of claims 6-8 have been cancelled herein, such that the rejection is now moot.

And, the terms "strong" and "powerful" in claims 12 and 56 were considered relative terms that rendered the claims indefinite. The claims as amended herein have removed these terms, such that the rejection is now moot.

Claims 4 and 49 were also rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite. The rejection is respectfully traversed.

Specifically, the Office Action stated that the claims were "ambiguous and unclear in that they do not state how HLA and the "attaching means" are structurally related." Applicants have amended claim 4 herein such that the relationship between the HLA and the attaching means is

now clear. Additionally, claim 49 has been cancelled herein, rendering the rejection moot as to claim 49.

For all of the reasons set forth above, the rejection of the claims under 35 U.S.C. §112, second paragraph are now moot. Accordingly, reconsideration and withdrawal of the §112 rejections is respectfully requested.

V. THE ART REJECTIONS ARE OVERCOME

Claims 1, 3, 4, 9, 11-14, 16-18, 26, 27, 29, 32, 33, 37, 46-50, 52, 53, 56, 57, 60, 63, 64, 67-70 and 75 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Patent No. 6,548,067 to Seeman *et al.* Claims 1, 3, 4, 9, 11-14, 16-18, 26, 27, 29, 32, 33, 37, 46-49, 51-53, 56, 57, 60, 63, 64, 67-70 and 75 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 6,548,067 to Seeman *et al.* in view of Neri *et al.* The rejections are respectfully traversed and will be addressed collectively.

It is respectfully asserted that a two-prong inquiry must be satisfied in order for a Section 102 rejection to stand. First, the prior art reference must contain all of the elements of the claimed invention. *See Lewmar Marine Inc. v. Barient Inc.,* 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987). Second, the prior art must contain an enabling disclosure. *See Chester v. Miller,* 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990). A reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. *See In re Donohue*, 226, U.S.P.Q. 619, 621 (Fed. Cir. 1985).

Turning to obviousness, it is also respectfully asserted that it is well-settled that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, "obvious to try" is not the standard under 35 U.S.C. §103. *In re Fine,* 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). And, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." Also, the Examiner is respectfully reminded that for the Section 103 rejection to be proper, **both the suggestion of the claimed invention and the expectation of success**

must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Applicants respectfully assert that the requirements for a Section 102 or 103 rejection are not met by either of Seeman or Neri, either alone or in any combination.

The Office Action alleges that Seeman "teaches a complex comprising an HLA class I molecule comprising a T cell binding portion and an attaching means for selectively attaching said HLA class I molecule to a target cell" and an attachment means comprising "a linking polypeptide with specific affinity for a molecule on the surface of the target cell, wherein the linking polypeptide is an antibody molecule that binds to an antigen on the target cell or a molecule that binds to a receptor on the cell." Office Action at 6. The Office Action also states that Seeman "teaches the binding of a recognition peptide (allodeterminatn) to the HLA class I molecule." Office Action at 6. Applicants respectfully disagree.

Contrary to the assertions in the Office Action, Seeman actually discloses class 1 MHC molecules linked to specific carrier molecules. The carrier molecules are linked to the MHC molecules via covalent N- or C- terminal linkages. Furthermore, Seeman does not describe the provision of recognition peptides for directing a T-cell response, nor does Seeman describe coupling of any attachment means to the MHC molecules. Thus, the pending claims are novel over Seeman.

Specifically, and as to the assertion that Seeman described the use of recognition peptides, it is first noted that this assertion is based mainly on figure 1 of Seeman, and the text in column 1. However, in figure 1, the α helices which are indicated by arrows in figure 1 (shown as α1 and α2) are, in fact, merely the allodeterminant regions of the HLA molecule of Seeman. Thus, they are not recognition peptides as required by the present invention. Specifically, they are not recognition peptides arranged to be presented by the HLA class 1 molecule as required by claim 1 herein since these regions are in fact part of the HLA class 1 molecule itself.

Indeed, this point is noted in the section of column 1 which the Office Action refers to (column 1, lines 58-62). It is explained here that αl, α2 and α3 are pointing to the α helices which carry the allodeterminants. Furthermore, in column 9, lines 40-44, also referenced by the Office Action, it is explained that $^{\alpha}1$, $^{\alpha}2$ and $^{\alpha}3$ denote the domains of a class 1 MHC antigen chain. Thus, it is clear from a careful reading of Seeman that no recognition peptides are disclosed, and in particular, no recognition peptides arranged to be presented by the HLA class 1

molecule are disclosed. Thus, the claims herein are novel over Seeman as the reference fails to recite each and every element of the pending claims.

Furthermore, the present invention is novel over Seeman for numerous other reasons. For example, the present invention seeks to exploit the immunological cytotoxic T-cell responses against particular recognition peptides. In contrast, the Seeman is concerned only with alloreactive responses.

Alloreactive responses are responses by the immune system against "foreign" HLA types. These can arise from malfunction of the elimination of self recognition from the immune system such as occurs in various diverse immune disorders, or may arise in other settings where foreign HLAs are introduced into a body, for example during transplant surgery. These immune responses, while often problematic in a clinical setting, are in fact weak and unreliable when applied to directed cell destruction. In contrast, by routing an immunological response through recognition peptides presented by HLA molecules as in the present invention, a significantly stronger and more reproducible response is achieved. Furthermore, the induction of the alloreactive responses of the are induced by very different chemical complexes than are the cytotoxic responses of the present invention.

Such alloreactive responses, as described in Seeman, do not employ recognition peptides. Indeed, the peptide presentation groove on the HLA molecule of Seeman's alloreactive systems will generally be unoccupied. Alloreactive responses are directed against sequences in the HLA molecules themselves. In contrast, independent claim 1 requires a recognition peptide and, in particular, requires it to be arranged to be presented in the HLA molecule. In stark contrast to the mechanism of response induction in Seeman, the complexes of the present invention induce the response based on this extra element-the recognition peptide-which is missing from Seeman. This physico-chemical difference is in fact recited in the pending claims, and is directly tied to the technical benefits of the use of the complexes of the present invention.

As previously stated, Seeman discloses class I MHC molecules linked to specific carrier molecules. The carrier molecules are linked to the MHC molecules via covalent N- or C-terminal linkages. Seeman does not describe the provision of recognition peptides for directing a T cell response, nor does Seeman describe coupling of any attachment means to the MHC molecule(s). Thus, the MHC entities of Seeman must be produced as single molecules. Seeman does not describe coupling of the carrier molecules to the MHC molecules.

Indeed, the features which distinguish pending claim 1 from Seeman include the requirement that the coupling system comprises a first small molecule joined to the linking polypeptide, and a second small molecule joined to the HLA class I molecule, wherein each of the first and second small molecules are each selected from biotin and avidin/streptavidin or calmodulin and calmodulin binding peptides. Furthermore, the claim requires the provision of a recognition peptide for presentation by the HLA molecule. These features are absent from Seeman as explained above.

The beneficial and practical effects of these differences include the fact that the complexes of pending claim 1 may be advantageously produced by serial addition of each of the components. This is made possible by the incorporation of the coupling system for joining the linking polypeptide to the class I HLA. In this manner, the complexes may be built up stepwise, avoiding the labor intensive chemistry and/or recombinant manipulations which would have to be performed if the complexes were assembled as single species as in Seeman.

Furthermore, the cytotoxic responses induced using the complexes of the present invention are different in nature, stronger and more reliable to the alloreactive responses with which Seeman is concerned. This is due to the recognition peptide feature of the invention.

Thus, a key benefit of the invention over the teachings of Seeman is to provide a targeted MHC complex which can be built up step-wise, alleviating the problems of producing large, covalently conjugated complexes as were previously described. Accordingly, the advantageous properties of the complexes of the present invention, which include the ability to assemble the parts of the complex in solution without the need to resort to crosslinking reagents, and the ability to direct immunologically relevant responses (rather than mere alloreactive responses) are neither taught nor suggested in the prior art.

Turning now to the obviousness rejection and Neri, it is respectfully submitted that this paper merely discloses scFv225.28S - calmodulin fusions. Again, there are no recognition peptides disclosed in Neri. Furthermore, there are no HLA molecules disclosed in Neri. The complexes and the compounds disclosed in Neri bear almost no relation to those disclosed in the present invention. Thus, the claims as amended are clearly novel over Neri. Furthermore, there is no teaching in Neri that would overcome the deficiencies of Seeman or which would provide one of skill in the art with the suggestion or motivation to modify Seeman utilizing the teachings

of Neri, irrespective of the fact that any such modification would not allow the skilled artisan to arrive at the present invention.

For example, and as described above, Seeman specifically places emphasis on the provision of MHC molecules as covalent fusions. The alleged advantageous properties of such complexes are repeatedly ascribed to the covalent conjugation of the different elements of those complexes. As described above, the present invention does not utilize such covalent conjugations. Thus, Seeman's conjugation method contains no direction or suggestion that would encourage one of skill in the art to modify the teachings of Seeman to arrive at the present invention. Indeed, Seeman clearly teaches away from the present invention by the emphasis placed on the covalent attachment which is absent from the present invention.

Accordingly, for all of the reasons set forth above, the present invention is novel and non-obvious over Seeman and Neri, either alone or in combination. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §§ 102 and 103 are respectfully requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, an interview, with supervisory review, e.g., with the Examiner, and the Examiner's SPE, is respectfully requested prior to issuance of any paper other than a Notice of Allowance. The Examiner is additionally respectfully requested to telephonically contact the undersigned to arrange a mutually convenient time and manner for the interview. The Examiner is also invited to telephonically contact the undersigned if there are any minor, formal issues that need resolving prior to issuance of a Notice of Allowance, with a view towards resolving such minor, formal issues via telephonic interview.

CONCLUSION

In view of these amendments and remarks, the application is in condition for allowance. Early and favorable reconsideration of the application, reconsideration and withdrawal of the objections and rejections, and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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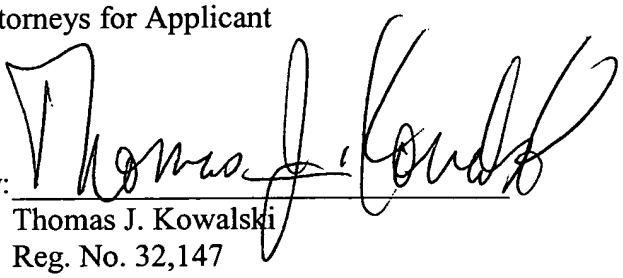
By: 

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